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Retrospective cohort study of risk-factors for esophageal cancer in Linxian, People's Republic of China

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A retrospective cohort study of esophageal (including gastric cardia) cancer was conducted to examine dietary and other potential risk factors in Linxian, a high-risk area in P.R. China. Study subjects were identified based on participation in a cytology examination conducted in 1974. They were interviewed in 1989 to obtain information on esophageal cancer risk-factors and identify new cases and deaths. A total of 1,162 subjects from the analytic cohort of 12,693 were determined to have developed esophageal cancer over the 15-year follow-up period. Results indicate that increased age, male gender, a positive family history, low education level, surface-water use, and pork consumption were the strongest risk factors for esophageal cancer identified in this cohort, while use of corn as a primary staple and infrequent consumption of fresh vegetables also were possible risk factors. Traditional or suspected risk factors for esophageal cancer in this and other populations—smoking and alcohol use, and pickled vegetable and moldy food consumption—were not risk factors in this study. Some variation in risk was seen based on the subject's cytology result from 1974. We conclude that dietary factors appear to play a role in the etiology of esophageal cancer in this high-risk population, but are less important than other constitutional factors such as age, gender, and family history.

Key words: Cohort study, cytology screening, diet, esophageal cancer, P.R. China.

Introduction

Linxian, a county in Henan Province of the People's Republic of China with a population of about 820,000, is located in north central China in the Taihang mountain area on the border of Henan, Hebei, and Shanxi provinces. The county covers an area of 2,100 square km, is mostly mountainous, and has an average annual rainfall of about 70 cm. The most common occupation (98 percent) is farming, with corn, wheat, and millet as the main crops. Annual rates of mortality from esophageal cancer in this area are the highest in the world, exceeding 100/100,000 person-years among both males and females, with cumulative death rates of persons to age 75 exceeding 20 percent in both sexes.[1] Esophageal cancer rates are highest in the northern half of the county and Yaocun commune has recorded rates among the highest of the northern communes—192/

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100,000 person-years for the 28-year period between 1959-87.[2]

There has been active scientific investigation of the causes of esophageal cancer in this region of China for over 30 years, and attention has focused on the potential roles of diet and genetics. The diet in Linxian is poor in fruits, vegetables, and animal foods with resultant inadequacies in intake of numerous vitamins and minerals. There are also special foods distinctive to Linxian which may play a role—picked vegetables which have been shown to be mutagenic and contain nitrosamines, and moldy foods containing mycotoxins. Physical trauma to the esophagus also may play a part, and silica fragments have been found in millet.[3] The etiologic factors responsible for most esophageal cancer in Western societies, *i.e.*, tobacco and alcohol, do not appear to play a prominent role in this cancer in China.

Of particular interest was a recent, large, case-control study conducted in Linxian in which no association was observed between pickled vegetable consumption and esophageal cancer.[4] No association was seen with moldy food consumption, but persons who reported eating more staples overall, and wheat and corn in particular, were more likely to have esophageal cancer.

The present study evaluated the relation of dietary and familial factors to esophageal cancer in Linxian. The study included two separate components: (i) a baseline cytological examination conducted in 1974; and (ii) a follow-up to ascertain cancer incidence and mortality as well as collect additional information about potential exposures conducted in 1989. A unique aspect of the evaluation was the information on cytologic status at the beginning of the follow-up.

Materials and methods

1974 mass screening

In August of 1974, scientists from the Cancer Institute of the Chinese Academy of Medical Sciences (Beijing) and Henan Medical University (Zhenzhou) jointly known as The Coordinating Group for the Research of Esophageal Carcinoma, conducted a population-based, esophageal balloon, cytology screening in Yaocun Commune, Linxian, Henan Province. At that time, the population of Yaocun Commune over 30 years of age was approximately 26,000, all of whom were invited to participate. Symptoms, family history, prior history of cancer, or other factors were not considered in the invitation to potential participants. Teams of cytologists and other medical workers went from village to village and performed the balloon swallows, using standard collection methods.[5] A total of 13,808 subjects (7,025 males and 6,783 females) participated in the 1974 balloon screening. The smears were stained with Papanicolaou stain, read, and classified into one of seven grades (normal; esophagitis; hyperplasia; dysplasia I; dysplasia II; suspicious for cancer; and cancer) as previously described.[6] Data recorded for each subject in 1974 included name, sex, age, cytology diagnosis, and an identification number. These data were keypunched in 1989 from the original 1974 record book in Yaocun Commune.

1989 follow-up study

In 1989, we attempted to obtain a follow-up interview on all subjects who participated in the 1974 mass screening. If a subject had died or moved away from Linxian, his or her closest available relative was interviewed. The interviews were performed by a team of 20 trained interviewers in the three-month period from November 1988 through January 1989. The interviewers were introduced individually to the subjects by their local barefoot doctor, and interviews were carried out in the subjects' homes. The interview obtained demographic information and included questions on vital status, cancer experience, smoking, alcohol consumption, diet, drinking water source, socioeconomic variables, and family history of cancer.

In 1989, 13,610 interviews were performed, representing 98.6 percent of the subjects screened in 1974. Sixty-eight percent of the interview respondents were the subjects who were screened in 1974; 12 percent were spouses of the subjects; 17 percent were other relatives; and three percent were non-relatives. To check the reproducibility of the interview results, an eight percent sample of subjects was selected randomly for re-interview. Of the subjects selected for sampling, 1,007 (92 percent) were successfully re-interviewed within one month of the original interview.

Medical records were sought for all interviewed subjects with evidence of any type of cancer or a record of death from any cause. A team of four trained abstractors used hospital records and death certificates to obtain information on vital status, cancer type, date and method of diagnosis of cancer, and date and cause of death. Death certificate information came from the Linxian Esophageal Cancer Institute, the repository for all vital statistics for the county. For patients with medical records, the date of the first admission with a cancer diagnosis was considered to be the cancer incidence date. For patients with only death certificate data available, the date of death was considered to be the cancer incidence date.

Throughout this paper, the term 'esophageal cancer' includes both esophageal and gastric cardia cancer.

Cancers arising in the gastric cardia have symptoms similar to those arising in the lower esophagus, and both of these tumors traditionally have been called 'esophageal cancer' in Linxian. This tradition was reflected in the 1989 interview answers, medical records, and death certificates, so accurate separation of these tumors could not be made with data from these sources.

Of the 13,610 interviewed subjects, 619 had technically unsatisfactory cytology smears, and 298 others had received a diagnosis of cancer before or during the 1974 screening. The analytic cohort for this study consisted of the 12,693 interviewed subjects with satisfactory cytology smears who were free of cancer at the beginning of the follow-up period. During the follow-up, a total of 1,162 new cases of esophageal cancer developed in this cohort, including 993 who died during this period. Medical abstracts were obtained on over 80 percent of both incident and mortal cases. In addition to esophageal cancer deaths, the analytic cohort experienced 246 deaths due to other cancers and 1,491 deaths due to non-cancer causes.

Accuracy of the interview data was checked by comparing interview and re-interview responses and by comparing interview and medical abstract data for questions which appeared in both sources. The concordance between interview and re-interview responses was high: 100 percent for vital status and type of incident cancer (esophageal cancer *cf* other cancers), and greater than 95 percent for year of death (± two years), cause of death (cancer *cf* other causes or esophageal cancer *cf* other causes), and most smoking, alcohol, dietary, socioeconomic, and family-history related questions. The concordance between interview and medical abstract data was also high: greater than 99 percent for vital status, and greater than 95 percent for type of cancer, year of death, and cause of death. When the same question appeared in both interview and abstract files, the response in the abstract file was used for analysis.

Risk factor information obtained from the interview in 1989 and used in these analyses included: age; sex; education (highest level attended); income (total income of household in 1974); cigarette use (ever regular use for more than six months); alcohol use (ever daily use for more than six months); primary drinking-water source before 1974 (shallow or deep well, pond, river); family history of esophageal or stomach cancer (in parents, sibs, children); history of regular moldy-food consumption in 1974 (yes/no); primary staple before 1974 (corn, millet, wheat, rice, sweet potato, other); primary cooking oil in 1974 (cottonseed, peanut, rapeseed, other); and frequency of consumption (never, occasional, regular) of selected dietary items before 1974, including corn, millet, wheat, rice, sweet potato, fresh fruit, dried fruit, fresh vegetables, dried vegetables, pickled vegetables, fried food, garlic, vinegar, pork, and eggs.

Statistical analysis

Descriptive statistics of the frequencies of variables were generated, based on all subjects in the analytic cohort with deletions as necessary for missing data. Age-specific, esophageal cancer incidence-rates for each sex were calculated by determining the number of cases which had occurred in each age and sex category and dividing that number by the number of person-years of observation in that category. Relative risks for risk factors (modeled as indicator variables) were calculated using SAS PROC PHGLM[7] with adjustment for age and sex alone, or in combination with selected other covariates. Confidence intervals of the regression coefficients were estimated assuming normal distributions of the estimates of the coefficients. Testing differences in risk across cytology categories was performed using models with interaction terms for the specific cytology category and risk factor of interest while controlling the main effects of the other cytology categories and all two-way interactions between the other cytology categories and other risk factors.

Results

The median age of the analytic cohort in 1974 was 44 years and nearly all were peasants. Table 1 shows the frequency of selected variables in the cohort as of 1974. Most subjects were poor and uneducated. One-third smoked, but less than one percent reported daily alcohol use. A family history of esophageal cancer was common. Corn was the dominant staple while cottonseed oil was the most frequently used cooking oil.

Consumption frequencies for specific dietary items are shown in Table 2. Corn was the most regularly consumed of the grains, followed by wheat. Fruits were eaten only occasionally, while vegetables were consumed regularly. Pickled vegetables were eaten commonly in 1974, but animal products were ingested only occasionally.

Table 3 shows age-specific, esophageal cancer incidence-rates for males and females in this cohort between 1974 and 1989. With the exception of 30-39 year olds, rates in males were 20-67 percent higher than in females, with an overall male to female ratio of 1.4. Rates increased progressively with age and approached 2.5 percent per year in males 60 or more years old.

Relative risks (age- and sex-adjusted) for selected risk factors and dietary items for esophageal cancer

incidence are shown in Table 4. A significant negative association was seen for persons with any (as opposed to no) education, in users of well—as opposed to surface—water, and in regular consumers of fresh vegetables, while risk was elevated among subjects with a positive family history and in persons who ate pork most frequently. There was a suggestion of an elevated risk among persons who reported corn as their primary staple. Smoking, alcohol, moldy foods, and pickled vegtables—prominant risk factors in other reports—were not identified as risk factors in this analysis.

Table 5 shows the relative risks for selected risk factors for esophageal cancer incidence determined from multivariate models, run separately for subjects with 1974 cytology results of 'Normal,' 'Hyperplasia' or 'Esophagitis,' and 'Dysplasia' or 'Suspicious for Cancer,' and for all subjects. In the model with all subjects, older age, being male, a positive family history, and pork consumption were significant risk factors, while education and well—as opposed to surface—water use were significantly protective. Regular consumption of fresh vegetables also appeared to be protective and use of corn as a primary staple appeared to be associated with increased risk, but neither of these associations

Table 1. Frequency of selected variables in 1974 in the study cohort from Linxian, P.R. China[a]

Variable	Percent[b]
Age (yrs)	
<30	4
30-39	32
40-49	30
50-59	23
60+	11
Sex	
Female	49
Male	51
Education (yrs)	
0	44
1-3	38
4-6	12
7+	5
Income (yuan)	
0	51
1-200	35
201-400	7
401+	7
Cigarette smoking (ever)	
No	67
Yes	34
Daily alcohol use	
No	99
Yes	1
Drinking water source	
Shallow well	88
Deep well	1
Pond	7
River	4
Family history of esophageal cancer	
No	71
Yes	29
Ate moldy food	
No	77
Yes	23
Primary staple	
Corn	95
Sweet potato	3
Wheat	1
Millet	1
Primary cooking oil	
Cottonseed	88
Peanut	7
Rapeseed	3
Other	3

[a] Number of subjects in each category varies from 12,355 to 12,693 due to missing data.
[b] Occasionally do not add to 100% due to rounding.

Table 2. Frequency of reported consumption of dietary items in 1974 among study cohort from Linxian, P.R. China (n = 12,693)

Dietary item	Frequency of consumption in 1974 (%)[a]		
	Never	Occasional[b]	Regular[c]
Corn	0	1	99
Millet	4	77	19
Wheat	0	44	56
Rice	17	82	1
Sweet potato	0	11	89
Fresh fruit	17	80	4
Dried fruit	50	50	1
Fresh vegetable	0	1	99
Dried vegetable	1	14	86
Pickled vegetable	34	24	43
Fried food	9	90	1
Garlic	2	52	46
Vinegar	2	70	28
Pork	11	89	0
Eggs	30	70	0

[a] Occasionally do not add to 100% due to rounding error.
[b] Occasional indicates less than once per month.
[c] Regular indicates once per month or more.

Table 3. Age- and sex-specific rates (per 100,000 person-years) of esophageal cancer incidence in Linxian, P.R.C., among study subjects, 1974-89

Age in 1974 (yrs)	Males	Females	All
<30	97	0	67
30-39	197	193	195
40-49	734	614	668
50-59	1,487	950	1,215
60+	2,418	1,447	2,007
All	836	585	710

Table 4. Age- and sex-adjusted relative risks (RR) and 95% confidence interval (CI) for selected, esophageal cancer incidence, risk factors and dietary items in Linxian, P.R. China

Variable	RR	(CI)[a]
Education (1 = any, 0 = none)	0.82	(0.71-0.94)[b]
Income (1 = > zero, 0 = zero)	1.05	(0.94-1.18)
Smoking (1 = ever, 0 = never)	0.96	(0.82-1.13)
Alcohol use (1 = daily, 0 = < daily)	0.50	(0.21-1.20)
Water use (1 = well, 0 = pond or river)	0.83	(0.69-0.99)[c]
Family history (1 = positive, 0 = negative)	1.92	(1.70-2.18)[d]
Regular moldy food use (1 = yes, 0 = no)	1.09	(0.95-1.24)
Primary staple (1 = corn, 0 = millet, wheat, or sweet potato)	1.27	(0.93-1.72)
Primary cooking oil (1 = cottonseed, 0 = rapeseed, peanut, or other)	1.05	(0.88-1.25)
Corn (1 = regular, 0 = occasional/never)	0.70	(0.38-1.26)
Millet (1 = regular, 0 = occasional/never)	0.96	(0.83-1.11)
Wheat (1 = regular, 0 = occasional/never)	0.96	(0.81-1.03)
Rice (1 = regular/occasional, 0 = never)	1.05	(0.90-1.22)
Sweet potato (1 = regular, 0 = occasional/never)	1.03	(0.85-1.24)
Fresh fruit (1 = regular/occasional, 0 = never)	0.99	(0.85-1.15)
Dried fruit (1 = regular/occasional, 0 = never)	1.02	(0.91-1.15)
Fresh vegetable (1 = regular, 0 = occasional/never)	0.66	(0.44-0.99)[e]
Dried vegetable (1 = regular, 0 = occasional/never)	0.99	(0.84-1.17)
Pickled vegetable (1 = regular, 0 = occasional/never)	1.03	(0.92-1.15)
Fried food (1 = regular/occasional, 0 = never)	0.92	(0.75-1.12)
Garlic (1 = regular, 0 = occasional/never)	1.00	(0.89-1.12)
Vinegar (1 = regular, 0 = occasional/never)	1.08	(0.95-1.23)
Pork (1 = regular/occasional, 0 = never)	1.37	(1.11-1.68)[f]
Eggs (1 = regular/occasional, 0 = never)	0.94	(0.83-1.07)

[a] All *P*-values > 0.10 unless otherwise noted.
[b] $P = 0.006$.
[c] $P = 0.038$.
[d] $P < 0.001$.
[e] $P = 0.044$.
[f] $P = 0.003$.

reached statistical significance ($P = 0.072$ and 0.090, respectively). The general pattern of risk (or protection) seen in all subjects was maintained in the cytology result-specific analyses, but some variation in risk by baseline cytology diagnosis was seen. Compared with the Hyperplasia and Dysplasia baseline-cytology groups combined, point estimates for being male, consuming corn as the primary staple, and pork consumption were somewhat higher in the Normal group, while the point estimate for well-water use was somewhat lower in the Normal group. The point estimate for fresh-vegetable use was lower in subjects with a cytologic diagnosis of Dysplasia or Suspicious for Cancer than in the other cytology categories combined. However, none of the point estimates for these risk factors was significantly different in one cytology category than the others ($P > 0.05$ for all comparisons).

Discussion

Results of this study indicated that increased age, male gender, a positive family history, low education level, surface-water use, and frequent consumption of pork were all significant, esophageal cancer risk-factors in this cohort, while use of corn as a primary staple and infrequent consumption of fresh vegetables were also possible risk factors. Traditional or suspected risk factors for esophageal cancer in this and other populations—smoking and alcohol use, and pickled vegetable and moldy food consumption—were not risk factors in this study. Some variation in risk was seen based on the subjects' cytology result from 1974. Most notably, the greatest benefit for regular use of fresh vegetables was seen in subjects with cytologic diagnoses of Dysplasia or Suspicious for Cancer.

Pickled vegetable consumption has been considered the most prominent, potential, contributing cause of esophageal cancer in Linxian because of its common consumption in the past, its demonstrated mutagenicity in *in vitro* studies, and the correlation of its consumption pattern with esophageal cancer rates among communes in several provinces in China.[8] The lack of risk for pickled vegetable consumption observed here, however, is consistent with the results from a recent large case-control study conducted in Linxian.[4] As further evidence against an etiologic role for pickled vegetables in esophageal cancer, there has been a dramatic decrease in reported use of pickled vegetables in

Table 5. Relative risks for selected risk factors for esophageal cancer incidence, 1974-89 in Linxian, P.R. China, categorized by 1974 cytology result

Risk factor	Relative risks (and 95% confidence intervals) by 1974 cytology result[a]			
	Normal (417/5,914)[b,c]	Hyperplasia or esophagitis (521/5,552)[d]	Dysplasia or suspicious for cancer (136/860)[e]	All (1,074/12,326)[f]
Age (yrs)	1.08 (1.07-1.09)	1.07 (1.06-1.08)	1.07 (1.05-1.09)	1.08 (1.07-1.08)
Sex (male)	2.04 (1.53-2.71)	1.47 (1.14-1.91)	1.24 (0.72-2.14)	1.63 (1.36-1.95)
Education (any)	0.78 (0.62-0.98)	0.78 (0.63-0.96)	0.88 (0.57-1.36)	0.79 (0.68-0.91)
Smoking (ever)	0.79 (0.61-1.01)	1.02 (0.80-1.29)	1.21 (0.74-1.99)	0.93 (0.79-1.09)
Well-water use	0.64 (0.49-0.85)	0.86 (0.66-1.13)	0.91 (0.51-1.63)	0.78 (0.65-0.93)
Family history (+)	2.10 (1.72-2.56)	1.86 (1.56-2.22)	1.89 (1.33-2.68)	1.96 (1.74-2.22)
Primary staple (corn)	1.53 (0.91-2.57)	1.31 (0.81-2.13)	1.06 (0.48-2.36)	1.32 (0.96-1.82)
Fresh-vegetable use (regular)	0.78 (0.35-1.76)	0.72 (0.40-1.32)	0.29 (0.10-0.84)	0.67 (0.44-1.04)
Pork use (regular or occasional)	1.46 (1.02-2.10)	1.36 (1.00-1.85)	1.27 (0.74-2.19)	1.37 (1.10-1.70)

[a] All relative risks are from multivariate models in which all nine variables shown in the table were included.
[b] Number of cases/number of total subjects in each cytology category.
[c] 156 observations deleted due to missing values.
[d] 177 observations deleted due to missing values.
[e] 34 observations deleted due to missing values.
[f] 367 observations deleted due to missing values.

Linxian since 1974 (likely because of the effectiveness of local propaganda denoting the potential harm of this food), but no parallel decrease in either incidence or mortality has been reported.[2,9]

The protective effect for consumption of fresh vegetables is in general agreement with that of previous epidemiologic studies conducted in both high- and low-risk areas.[10-15] A notable exception is the case-control study conducted in Linxian which did not find a benefit for fresh vegetable ingestion.[4]

Persons who consumed pork regularly or occasionally were at increased risk, and persons reporting corn as their primary staple showed a marginal increase in esophageal cancer risk when compared with persons whose primary staple was wheat, millet, or sweet potato. These results were similar to that of the recent case-control study in which fairly strong associations for risk of esophageal cancer were seen for both pork consumption and intake of wheat and corn.[4] The result of our study was also consistent with studies from South Africa and Italy which have seen an elevated risk in subjects with higher wheat and corn consumption.[16-18]

Despite previous reports identifying carcinogens in moldy corn (and cornmeal), pickled vegetables, and other moldy food, and the association of *Fusarium moniliforme* contamination in corn with the prevalence of esophageal cancer in South Africa and in China, consumption of moldy food in the present study was reported no more frequently among persons who subsequently developed esophageal cancer than among persons who did not develop the disease.[8,19,20]

Our data indicate a significant reduction in risk associated with drinking well—as opposed to surface—water. This result is the opposite of that from another study conducted in Linxian in which groundwater use was associated with increased risk.[21] No association of water source with esophageal cancer risk was seen in the case-control study from Linxian.[4] The elevated risk observed for surface water may be related to a higher nitrate content in that water, since nitrate content in drinking water has been shown to decrease from high- to low-risk areas.[22]

Smoking was not a risk factor in this study (Table 5). Because only a few women in this cohort smoked, it is clear that the high esophageal cancer rates experienced

by these women cannot be due to smoking. The results from the recent case-control study found smoking to be a mild risk factor in low- but not high-risk villages in Linxian.[4] Alcohol consumption was not evaluable because less than one percent of the study population reported drinking alcohol.

Although environmental factors have been considered to be the major contributors to esophageal cancer in China, the consistent finding of an increased risk associated with family history in this and other studies conducted in Linxian, as well as in studies conducted in nearby Shanxi Province where disease rates are elevated, suggests that genetic factors also may play an important role in the development of this cancer.[4,23-26] Familial aggregation can be due to environmental as well as genetic factors, but the finding from a recent segregation analysis among high-risk families from Linxian—that disease transmission was most compatible with an autosomal recessive trait—lends further credence to the genetic hypothesis.[27]

A unique feature of these data was the existence of baseline esophageal cytology diagnoses on all subjects. Examination of risk factors by these baseline diagnoses showed some differences which allowed us to speculate on the potential role of these risk factors at different stages in carcinogenesis. Risk associated with some factors such as age, education, and family history were the same for all cytology categories. The risk associated with some other factors, however, did appear to vary by baseline diagnosis, although none of these differences were statistically significant. The protective effect of well-water use, for example, appeared strongest in the Normal group, suggesting that factors found in water may act early in carcinogenesis. A similar early effect may be hypothesized for male gender, for consuming corn as the primary staple, and for pork consumption, where the greatest risks also appeared to be among the Normal category. In contrast, fresh vegetable use appeared most protective among subjects with cytologic diagnoses of Dysplasia or Suspicious for Cancer, suggesting that even at this late stage some benefit may be achieved from dietary change.

There were several potentially important shortcomings in the present study. First, information on risk factors was collected retrospectively and, in many cases (including all persons who died of esophageal cancer), from secondary sources. Second, there was little variation in exposure for a number of putative esophageal cancer risk-factors. The homogeneity of exposure in this high-risk population was striking for a number of potential risk factors, both dietary and nondietary. Third, quantitation of the exposures under study was limited and no objective measurements were available to confirm exposures. Finally, although reproducibility was assessed, no validation (biologic or epidemiologic) was performed of the questionnaire used to collect exposure data. Several of these shortcomings, at least as they relate to dietary risk factors, may have been muted, however, by the generally limited change in diet over the years in this area, which suggests that the retrospective reporting, even from secondary sources, was reasonably credible. Accurate reporting for some items may not have occurred, however, because of concerted public awareness campaigns since the 1960s regarding such items as pickled vegetables and moldy food. Differential underreporting of consumption of these foods by cases may have contributed to the lack of association observed between them and disease. Finally, although most cases had medical records, diagnoses usually did not distinguish between esophageal and cardia cancer.

Despite these weaknesses, this study has a number of strengths, and it benefits from the completeness of the follow-up effort, the large number of events observed during follow-up, and the availability of baseline cytology diagnoses.

In conclusion, dietary factors appear to play a role in the etiology of esophageal cancer in this high-risk population, but are less important than other constitutional factors such as age, gender, and family history of cancer.

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References

1. Li JY. Epidemiology of esophageal cancer in China. *Natl Cancer Inst Monogr* 1982; **62:** 113-20.
2. Zhang ZX, Li BY, Jin SS. Epidemiologic trends of esophageal cancer in Linxian [in Chinese]. *Research on Esophageal Cancer Prevention and Treatment* (Shi Guan Ai Fang Zhi Yan Jiu—Linxian) 1990; **1:** 1-14.
3. O'Neill C, Pan QQ, Clarke G, *et al.* Silica fragments from millet bran in mucosa surrounding oesophageal tumors in patients in northern China. *Lancet* 1982; **1:** 1202-6.
4. Li JY, Ershow AG, Chen ZJ, *et al.* A case-control study of cancer of the esophageal and gastric cardia in Linxian. *Int J Cancer* 1989; **43:** 755-61.
5. Shu YJ. Cytopathology of the esophagus: an overview of esophageal cytopathology in China. *Acta Cytologica* 1986; **27(1):** 7-16.

6. Dawsey SM, Yu Y, Taylor PR, *et al.* Esophageal cytology and subsequent risk of esophageal cancer: a prospective follow-up study from Linxian, China [submitted].
7. SAS Institute Inc. *SAS User's Guide; Statistics, 1985 ed.* Cary, NC: SAS Institute, 1985.
8. Yang CS. Research on esophageal cancer in China: a review. *Cancer Res* 1980; **40:** 2633-44.
9. Lu JB, Yang WX, Liu JM, Li YS, Qin YM. Trends in morbidity and mortality for esophageal cancer in Linxian County, 1959-1983. *Int J Cancer* 1985; **36:** 643-5.
10. Yu MC, Garabrant DH, Peters JM, Mack TM. Tobacco, alcohol, diet, occupation, and carcinoma of the esophagus. *Cancer Res* 1988; **48:** 3843-8.
11. Yang CS, Miao Y, Yang W, *et al.* Diet and vitamin nutrition of the high oesophageal cancer risk population in Linxian, China. *Nutr Cancer* 1982; **4:** 154-64.
12. De Carli A, Liati P, Negri E, Francheschi S, La Vecchia C. Vitamin A and other dietary factors in the etiology of oesophageal cancer. *Nutr Cancer* 1987; **10:** 29-37.
13. Brown LM, Blot WJ, Schuman SH, *et al.* Environmental factors and high risk of esophageal cancer among men in coastal South Carolina. *JNCI* 1988; **80:** 1620-5.
14. Ziegler RG, Morris LE, Blot WJ, Pottern LM, Hoover R, Fraumeni JF, Jr. Esophageal cancer among black men in Washington, DC. II. Role of nutrition. *JNCI* 1981; **67:** 1199-206.
15. Mettlin C, Graham S, Priore R, Marshall J, Swanson M. Diet and cancer of the esophagus. *Nutr Cancer* 1981; **2(3):** 143-7.
16. Van Rensburg SJ, Benade AS, Rose EF, Du Plessis JP. Nutritional status of African populations predisposed to esophageal cancer. *Nutr Cancer* 1983; **4:** 206-15.
17. Van Rensburg SJ, Bradsham ES, Bradsham D, Rose EF. Oesophageal cancer in Zulu men in South Africa: a case-control study. *Br J Cancer* 1985; **51:** 399-405.
18. Franceschi S, Bidoli E, Baren A, LaVecchia C. Maize and risk of cancer of the oral cavity, pharynx, and esophagus in northern Italy. *JNCI* 1980; **82:** 1407-11.
19. Li MX, Ji C, Cheng SI. Occurrence of nitroso compounds in fungi-contaminated foods: a review. *Nutr Cancer* 1986; **8:** 65-9.
20. Marasas WFO, Jaskiewicz K, Venter FS, Van Schalkwyk DJ. Fusarium moniliforme contamination of maize in oesophageal cancer areas in Transkei. *S Afr Med J* 1988; **74:** 110-4.
21. Lu JB, Yang WX, Dong WZ, Sang JY. A prospective study of esophageal cytological atypia in Linxian County. *Int J Cancer* 1988; **41:** 805-8.
22. Department of Chemical Etiology and Carcinogenesis. Preliminary analyses of the distribution of esophageal cancer mortality rates, the geographical environment, and the chemical elements in food and drinking water in Anyang district, Henan Province [in Chinese]. *Chin J Oncol* 1980; **2(1):** 29-37.
23. Wu M, Wang X, Zhu A, Shao L. Distribution of ABO blood groups among patients with carcinoma of the esophagus and gastric cardia in Linxian People's Hospital [in Chinese]. *Chin J Oncol* 1981; **3:** 16-8.
24. Hu N, Dawsey SM, Wu M, Taylor PR. Family history of esophageal cancer in Shanxi Province, China. *Eur J Cancer* 1991; **27(10):** 1336.
25. Li GH, He LJ. A survey of the familial aggregation of esophageal cancer in Yangcheng County, Shanxi Province. In: Wagner G, Zhang YH, eds. *Cancer of the Liver, Esophagus, and Nasopharynx*. New York: Springer-Verlag, 1987; 114-8.
26. Hu N, Dawsey SM, Wu M, Bonney GE, *et al.* Familial aggregation of esophageal cancer in Yangcheng County, Shanxi Province, China. *Int J Epidemiol* 1992; **21:** 877-82.
27. Carter CL, Hu N, Wu M, Lin PZ, Murigande C, Bonney GE. Segregation analysis of esophageal cancer in 221 high risk Chinese families. *JNCI* 1992; **84:** 771-6.